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# Bioactive alkaloids from the venom of Dendrobatoidea Cope, 1865: a scoping review

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**ABSTRACT**

Bioactive compounds derived from secondary metabolism in animals have refined selectivity and potency for certain biological targets. The superfamily Dendrobatoidea is adapted to the dietary sequestration and secretion of toxic alkaloids, which play a role in several biological activities, and thus serve as a potential source for pharmacological and biotechnological applications. This article constitutes a scoping review to understand the trends in experimental research involving bioactive alkaloids derived from Dendrobatoidea based upon scientometric approaches. Forty-eight (48) publications were found in 30 journals in the period of 60 years, between 1962 and 2022. More than 23 structural classes of alkaloids were cited, with 27.63% for batrachotoxins, 13.64% for pyridinics, with an emphasis on epibatidine, 16.36% for pumiliotoxins, and 11.82% for histrionicotoxins. These tests included *in vivo* (54.9%), *in vitro* (39.4%), and *in silico* simulations (5.6%). Most compounds (54.8%) were isolated from skin extracts, whereas the remainder were obtained through molecular synthesis. Thirteen main biological activities were identified, including acetylcholinesterase inhibitors (27.59%), sodium channel inhibitors (12.07%), cardiac (12.07%), analgesic (8.62%), and neuromuscular effects (8.62%). The substances were cited as being of natural origin in the "Dendrobatidae" family, genus "*Phyllobates*," "*Dendrobates*," and seven species: *Epipedobates tricolor*, *Phyllobates aurotaenia*, *Oophaga histrionica*, *Oophaga pumilio*, *Phyllobates terribilis*, *Epipedobates anthonyi*, and *Ameerega flavopicta*. To date, only a few biological activities have been experimentally tested; hence, further studies on the bioprospecting of animal compounds and ecological approaches are needed.

**KEYWORDS**

Biodiversity; poison frogs; secondary metabolites; toxins; biotechnological

## Introduction

Natural products are sources of bioactive compounds with a significant potential for pharmacological and biotechnological applications (Atanasov et al. 2021; Bauer and Bronstrup 2014; Furtado et al. 2022; Wainwright et al. 2022; Wu et al. 2020). The diversity of bioactive molecules found in animals is high; however, few compounds have been explored or recognized (Bordon et al. 2020; Chen et al. 2018; Izzati et al. 2021).

A significant gap exists in scientific knowledge regarding animal toxins, although these compounds exhibit refined biological actions in terms of selectivity and potency (Acunha et al. 2023; Sakamoto and Ishikawa 2022; Santos et al. 2021; Slagboom et al. 2022; Souza et al. 2018; Tan 2022; Zhang 2015). Compounds derived from animals are important tools for developing drugs for the treatment of various diseases (Barros et al. 2022; Bordon et al. 2020; Caty et al. 2019; Ferreira, Arcanjo, and Peron 2023; Fox and Serrano 2007; Gutiérrez, Morales, and Pino 2018; Newman and Cragg 2020; Souza et al. 2018).

Alkaloids have been widely used for bioprospecting owing to their pharmacological potential for drug production to combat diseases initiated by viruses, such as Chikungunya, Coxsackievirus, Dengue, Ebola, Influenza, Hepatitis, Herpes, Human Immunodeficiency Virus, and Covid-19, in addition to other diseases such as liver fibrosis,

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cancer, Alzheimer's disease, and diabetes (Cely-Veloza, Kato, and Coy-Barrera 2023; Cordell, Quinn-Beattie, and Farnsworth 2001; Islam and Mubarak 2020; Shan et al. 2019; Souza et al. 2018; Zhang et al. 2020).

In Amphibia Gray, 1825, few bioprospecting studies of compounds and tests of biological activities were undertaken and the findings of these studies demonstrate the diversity of poisons in this group. The integument of anurans is a source of bioactive compounds that are secreted to protect against predators, parasites, and pathogens (Mans et al. 2021; Spinelli et al. 2019). The superfamily Dendrobatoidea (Cope, 1865) in the Order Anura (Fischer von Waldheim, 1813) is a monophyletic clade that is endemic to mountainous areas in the neotropics, with over 100 species known for the sequestration of alkaloids and physiological adaptation to chemical defenses through skin secretion (Grant and Frost 2016). Numerous alkaloids were identified in Dendrobatidae, totaling over 500 types, some of these species possessing the remarkable ability to modify the alkaloid structures acquired from their diet, resulting in even more potent and toxic variants (Saporito et al. 2012).

Within this group, the genus *Phyllobates* Duméril and Bibron, 1841 stands out for its species that secrete highly toxic alkaloids, including the infamous batrachotoxin (Mebs et al. 2014). In addition, alkaloids such as decahydroquinolines, pumiliotoxins, and histrionicotoxins exhibit inhibitory effects on bacterial cultures such as *Escherichia coli* (Migula 1895) Castellani and Chalmers 1919 (Approved Lists 1980), *Bacillus subtilis* (Ehrenberg 1835) Cohn 1872, and the fungus *Candida Albicans* (C.P. Robin) Berkhout (1923) (Mina et al. 2015). Notably, specific alkaloids such as pumiliotoxin were found to repel *Aedes aegypti* (Linnaeus, 1762) mosquitoes (Weldon et al. 2006).

A literature review of the bioactive compounds in Dendrobatidae conducted by Daly et al. (1982) indicated the promise of at least 5 classes of alkaloids for pharmacological studies. The study and utilization of natural resources, especially pharmacological sources, may play an important role in the emergence of commercial bioproducts, such as (1) detection and identification of prototypes, (2) presence of chemical precursors, and (3) discovery of compounds for further synthesis, which eventually contribute to scientific and technological development (Barreiro and Bolzani 2009, Newman et al. 2020; Sakamoto and Ishikawa 2022; Scherlach and Hertweck 2021).

According to Ferreira et al. (2023), the use of natural products from animal sources needs to be considered fundamental from a social and economic perspective for the scientific and commercial progress of tropical countries. Recognizing biodiversity and its natural products as a pharmaceutical library enables the establishment of sustainable guarantees for the bioeconomic chain. Biotechnological production generates goods that not only enhance the quality of life in societies, but also add value and provide tangible justifications for the protection of natural resources (Astolfi-Filho, Silva, and Bigi 2014; Scherlach and Hertweck 2021).

Thus, this study conducted a scoping review of the literature focusing on scientometric analysis to examine the state-of-the-art research over the last 60 years. The primary objective was to understand the research trends related to bioassays with alkaloids present in the Dendrobatoidea group, and to explore their potential for bioprospective analyses in the field of pharmaceuticals. Secondly, this investigation sought to answer the following questions: How much research has been conducted in this field of analysis and in what areas? Which chemical compounds were generally used in the experiments, and how were these compounds obtained? Which biological activities were mainly tested in these bioassays? Which taxonomic groups are referenced in the studies? Addressing these questions may aid in identifying gaps in the knowledge within the field of natural products of animal origin and guide further research development in this promising area.

## Materials and methods

### *Search strategy*

This research adopted a descriptive basis with a quantitative approach, aiming to evaluate the current state of the art in the field of anuran alkaloids from the Superfamily Dendrobatoidea,

with a scientometric bias. The literature reviewed spanned up to August 2022. To gather relevant information, documents were retrieved from reputable academic databases, including Google Scholar, PubMed, Web of Science, and Scopus.

The organization of the research was carried out through the structuring defined by PRISMA for Scoping (Prima-Scr) according to Tricco et al. (2018), considering its conceptual definitions for structuring the research, justifications, protocol, PICO objective, research, organization of results, critical analysis of information, and conclusions.

The systematic organization of data following these methodologies ensured a structured approach to data collection and analysis, thus facilitating a comprehensive understanding of research trends and advances in the study of the bioactive products of anuran alkaloids within the Dendrobatoidea Superfamily. This study is an update on Daly's (1982) study.

### *Eligibility*

The search stages followed the systematization presented in Figure 1. Studies selected were published in English. During data refinement, duplicate files of the same size, name, and content were excluded. Review articles, synthesis of molecules, differentiated taxonomic groups, tests of ecological biological activities, and incomplete investigations were excluded. Unpublished academic works such as theses or dissertations were not considered. However, studies on tests of artificially synthesized molecules in which Dendrobatoidea species were referenced were considered for the review.

The systematic searches were performed from groups from differing arrangements by Boolean

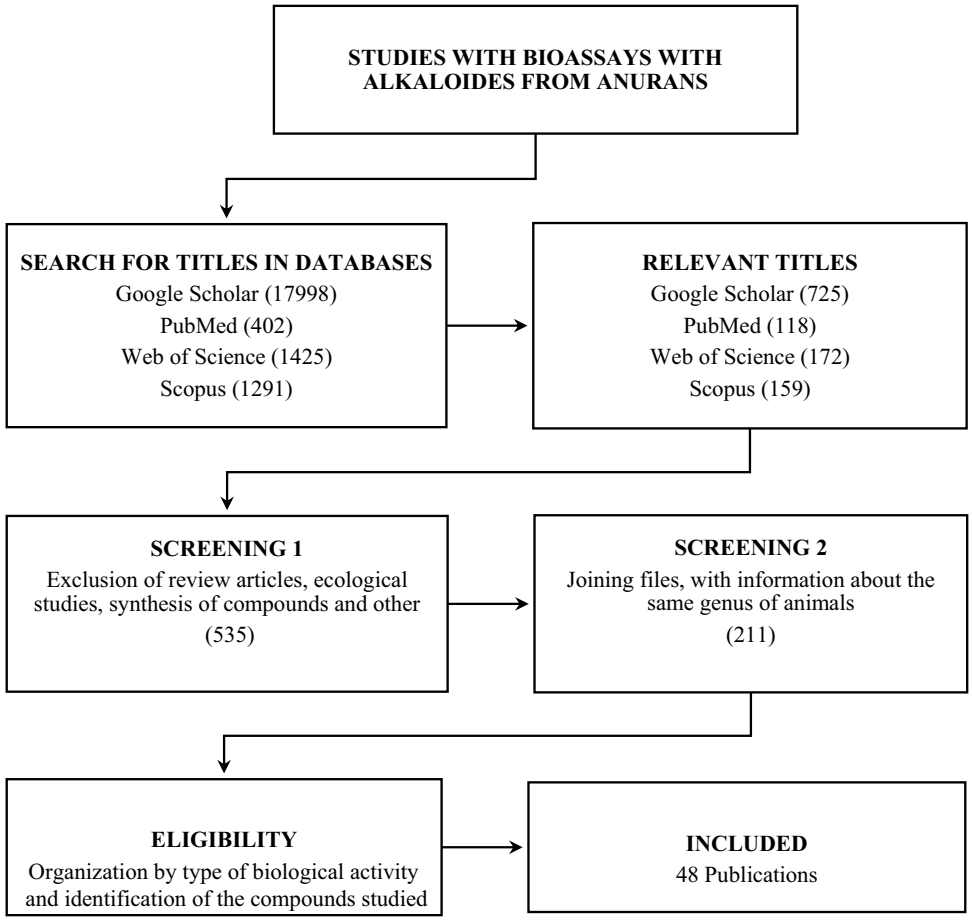


**Figure 1.** Flowchart on the refinement of information obtained in the database for inclusion in the study.

connectives "AND" and "OR" using the terms: "*Ameerega*" OR "*Colostethus*" OR "*Epipedobates*" OR "*Silverstoneia*" OR "*Adelphobates*" OR "*Dendrobates*" OR "*Excidobates*" OR "*Minyobates*" OR "*Oophaga*" Or "*Phyllobates*" OR "*Ranitomeya*" OR "*Hyloxalus*" OR "*Mannophryne*" OR "*Aromobates*" OR "*Rheobates*" OR "*Anomaloglossus*" OR "*Allobates*" AND "alkaloid" OR "bioactive" OR "venom," with results selected using the inclusion criteria.

### Data screening

The screening process involved a comprehensive examination of the titles, abstracts, results, and conclusions of the selected documents, adhering to the predefined criteria for inclusion. After meticulous analysis, relevant findings were integrated into the results section. The technique used for this quantitative description ensured a systematic and comprehensive presentation of data obtained from the reviewed literature.

### Data extraction and analysis

The process of searching and screening data was conducted independently by two members of the team. The inconsistencies and weightings were discussed in data evaluation meetings, in which results were calibrated to evaluate duplicates. In addition, studies that were inconsistent with the objectives of the proposal, incomplete, gray literature, did not mention the groups studied, or discussed related topics, such as the chemical synthesis of the compounds studied, were also screened.

The variables used for the measurements were tabulated using Excel software: (i) title, (ii) author, (iii) date of publication, species where the compound or its congener was found, (iv) alkaloid class, (v) biological activity of alkaloids, (vi) type of bioassay, and (vii) form of the compounds. The descriptive characteristics and results of each investigation were extracted from the tables.

Following the composition of genera described by Grant and Frost (2016), with the scientific nomenclature revised in Brands (2022): "*Ameerega*" Bauer, 1986; "*Colostethus*" Cope, 1866; "*Epipedobates*" Myers, 1987; "*Silverstoneia*" Grant, Frost, Caldwell, Gagliardo, Haddad, Kok, Means, Noonan, Schargel & Wheeler, 2006; "*Adelphobates*" Grant, Frost, Caldwell, Gagliardo, Haddad, Kok, Means, Noonan, Schargel & Wheeler, 2006; "*Dendrobates*" Wagler, 1830; "*Excidobates*" Twomey & Brown, 2008; "*Minyobates*" Myers, 1987; "*Oophaga*" Bauer, 1994; "*Phyllobates*" Duméril & Bibron, 1841; "*Ranitomeya*" Bauer, 1986; "*Hyloxalus*" Jiménez de la Espada, 1870; "*Mannophryne*" La Marca, 1992; "*Aromobates*" Myers, Paolillo-O. & Daly, 1991; "*Rheobates*" Grant, Frost, Caldwell, Gagliardo, Haddad, Kok, Means, Noonan, Schargel & Wheeler, 2006; "*Anomaloglossus*" Grant, Frost, Caldwell, Gagliardo, Haddad, Kok, Means, Noonan, Schargel & Wheeler, 2006; "*Allobates*" Zimmermann & Zimmermann, 1988.

The selected biological activities followed a pattern similar to the definitions of biological activity demonstrated by amphibian-secreted substances as described by Daly and Myers (1967), with the addition of others. The alkaloid class was based upon the methods described by Daly et al. (1993) and Saporito et al. (2012). The drawings of spatial structures in the program Chem Basic were performed based upon investigation found in the research results or from basic studies on alkaloids, such as Daly et al. (1993, 2005), compared to PubChem (https://pubchem.ncbi.nlm.nih.gov/). The observations were structured in tables and graphic figures, and word clouds were elaborated using Infogram software (https://infogram.com/app).

## Results and discussion

### Scientific studies

After screening the titles, 48 publications that conducted experiments with bioactive alkaloids present in Dendrobatoidea anurans met the inclusion criteria. These investigations date back 60 years, covering the period between 1962 and 2022 and are distributed with a maximum of three (3) publications each year. The selected publications were published in 30 journals, with only "Proceedings of the National Academy of Sciences" (12.7%), "Toxicon" (10.6%), "Journal of Natural Products" (6.3%), and "European Journal of Pharmacology" (6.3%) publishing three or more articles related to this topic.

In amphibians, the venom is composed of a complex mixture of secondary metabolites developed over thousands of years in response to biological and ecological stressors, such as arm race

defenses in trophic networks (Barros et al. 2022; Mans et al. 2021; Rodríguez-Saona 2012; Scherlach and Hertweck 2021). Dendrobatoidea skin alkaloids were studied for at least 60 years; however, the largest number of investigations, including the most current ones, are directed toward the origin and identification of compounds and other aspects of chemical ecology, such as seasonal variation of the alkaloid profile in different populations, as well as physiological aspects related to absorption, tolerance, and maintenance of compounds in the body. Nevertheless, assessment of biological (Basham et al. 2021; Caty et al. 2019; Gonzalez et al. 2021; Jeckel et al. 2019, 2022; Protti-Sánchez et al. 2019) and pharmacological activities were considered in relatively few studies.

Although bioprospecting advances in bioactive compounds secreted by Dendrobatidae anurans are well-established, the number of scientific publications involving biological activity experiments still proved to be low with a deficit in the number of alkaloids already discovered in the group, especially when compared with the analysis conducted by Daly et al. (**1982**). However, it should be noted that there has been a marginal increase in the number of publications in this field.

Alkaloids are a rich class of secondary metabolites that are known for their effective biological activity and diverse applications and were found to be crucial components for the future production of medicines, making them an essential focus of research in pharmaceutical development (Abookleesh, Al-Anzi, and Ullah 2022; Ajebli, Khan, and Eddouks 2021; Scherlach and Hertweck 2021; Seteyen et al. 2022; Wainwright et al. 2022).

Drugs based upon animal toxins may generate millions of dollars, leading to the development of agents with multiple or promising targets for various groups of diseases (Atanasov et al. 2021; Bauer and Bronstrup 2014; Caty et al. 2019; Ferreira, Arcanjo, and Peron 2023; Scherlach and Hertweck 2021; Spinelli et al. 2019; Wu et al. 2020). These compounds are bioactive with wide structural diversity, specific effects, and multi-target actions and exhibit significant potential for development of new bioprospective targets for therapeutic purposes (Sakamoto and Ishikawa 2022; Souza et al. 2018).

### *Biological activity tests*

Biological activity tests were performed on at least 23 structural classes of alkaloids. Among these, there was a notable citation frequency of 21.82% for batrachotoxins, 16.36% for pumiliotoxins, 13.64% for pyridinic alkaloids, with a specific emphasis on epibatidine, and 11.82% for histrionicotoxins (Figure 2).

The remaining alkaloids, including pyrrolidine, piperidine, indolizidine, decahydroquinoline, and gephyrotoxins, were distributed in groups with comparatively lower citation frequencies. These findings emphasize the diversity of alkaloids tested for their biological activities and the significance of specific structural classes illustrated in Figure 3.

Within Dendrobatidae, more than 500 types of alkaloids have been described in at least 25 structural classes, with compounds acquired by (1) feeding on arthropods, (2) compounds that are fully sequestered, or (3) undergoing slight modifications. Those compounds include alkaloids, histrionicotoxins, pumiliotoxins, decahydroquinoline, quinolines, indolizidines, quinolizidenes, pyrrolizidenes, and pyrrolidines (Saporito et al. 2012). Daly et al. (**1982**) reported the presence of at least 5 classes of alkaloids with pharmacological properties. Thus, several classes of alkaloids were examined in bioassays for biological activities, despite the limited number of publications.

Indolizidine alkaloids, quinolizidines, and pyrrolidine exhibited biological antibacterial, antifungal, anti-inflammatory, antimalarial, antiparasitic, antiplatelet, antitumour, antiviral, cardiovascular-protective, insecticide, neuroprotective, antidiabetic, and anti-Alzheimer's disease properties (Ajebli, Khan, and Eddouks 2021, Cely- Veloza, Kato and Coy-Barrera, **2023**; Islam and Mubarak 2020; Zhang et al. 2020).

The tests used in the studies comprised the following methods: *in vivo* (54.9%), *in vitro* (39.4%), and *in silico* (5.6%). Compounds isolated from skin extracts accounted for 54.8% of cases, whereas the remaining compounds were obtained through molecular synthesis. In some tests, a mixture of toxic compounds was used to conduct bioassays. Although *in vivo* experimentation initiated moral debates regarding animal use, it is important to explore suitable alternatives, such as conducting

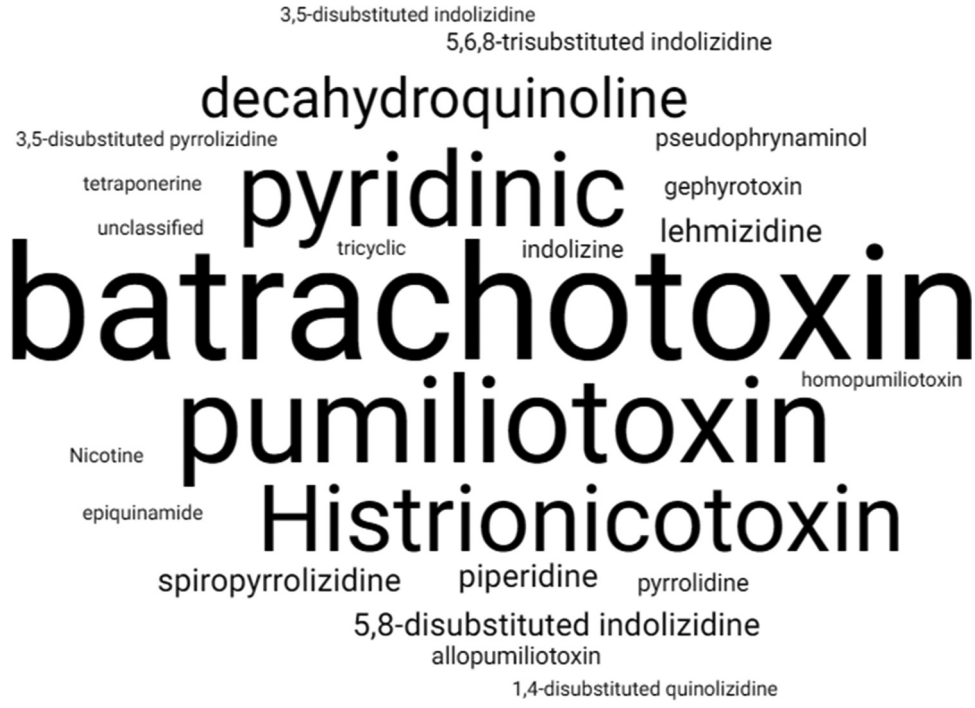


**Figure 2.** Word cloud with the proportion of use of the chemical compounds from Dendrobatoidea in tests of biological activities over the last 60 years.

more *in silico* tests to examine the activity of compounds. Emphasising the use of *in silico* methods may provide valuable insights into potential ethical concerns (Atanasov et al. 2021; Bordon et al. 2020; Tan 2022).

Studies on the bioactive molecules of anuran alkaloids related to biotechnological innovation might contribute to science in different ways, either as a basis for testing diagnostic tools or as experimental molecules for the validation of postulated therapeutic targets, drug libraries, prototypes for drug planning, and therapeutic agents (Barreiro and Bolzani 2009; Bauer and Bronstrup 2014; Chen et al. 2018; Ferreira, Arcanjo, and Peron 2023; Fox and Serrano 2007; Gotti et al. 2000; Gutiérrez, Morales, and Pino 2018; Newman and Cragg 2020; Slagboom et al. 2022; Souza et al. 2018).

### *Biological activities*

The biological activities identified in this investigation encompassed 13 main mechanisms: acetylcholinesterase inhibition (27.5%), analgesic (8.62%), anticancer (3.45%), antimicrobial (5.17%), cardiac (12.07%), insecticidal (6.9%), intestinal musculature (1.72%), effects on the nervous system (8.62%), neuromuscular (5.17%), respiratory muscle (1.72%), effects on sodium channels (12.07%), teratogenicity (1.72%), and general toxicity (5.17%) (Figure 4).

Animal toxins perform important biological activities (Souza et al. 2018). Batrachotoxin, a natural compound with the chemical formula (3α,5β,6α,14α,15β,16β)-20-(3-amino-3-carboxypropyl)-14,15-epoxy-5,6-dihydro-3-hydroxy-16-(methylamino) stigmastane-3,14-diol), was noted to be bioactive for 12 of the 13 reported activities. Batrachotoxin is a steroidal alkaloid consisting of intricate steroid rings with a highly reactive guanidine-containing side chain. The three-dimensional structure of batrachotoxin is crucial for its potent and toxic biological activity (Tokuyama, Daly, and Witkop 1969). According to Bosmans et al. (2004), batrachotoxin and its metabolites, detected in *Phyllobates*, have emerged as important compounds of technological applicability as these compounds specifically act on the $Na^+$ voltage channels by (1) increasing the rate of uptake of this ion, and (2) acting in the regulation or prevention of inactivation of nerve and muscle cells. Consequently, these actions exhibit potential for analgesic use, regardless of the restrictions attributed to severe

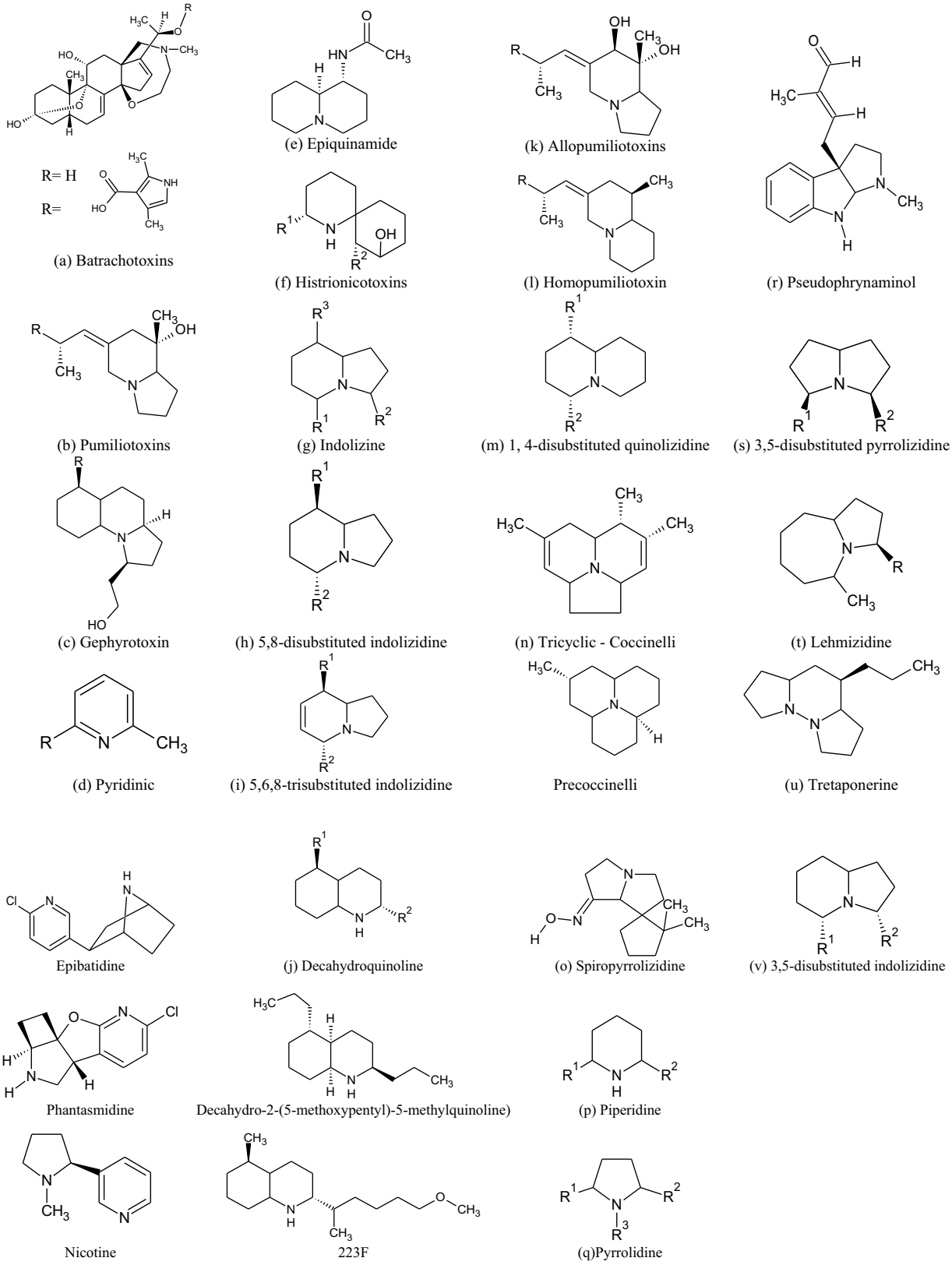


**Figure 3.** Chemical structures of Dendrobatoidea venom alkaloids tested in biological activity experiments, indicated by letters in table I, followed by references: (a) batrachotoxins (MacFoy et al. 2005); (b) pumiliotoxins (Daly, Garraffo, and Spande 1993); (c) gephyrotoxin (Daly, Spande, and Garraffo 2005); (d) pyridinic (MacFoy et al. 2005), epibatidine (Daly, Garraffo, and Spande 1993), phantasmidine (Fitch et al. 2010), nicotine (Daly, Spande, and Garraffo 2005); (e) epiquinamide (Fitch et al. 2003); (f) histrionicotoxins (Daly, Garraffo, and Spande 1993); (g) Indolizina (PubChem: https://pubchem.Ncbi.nlm.nih.gov/#query=indolizine); (h) 5,8-disubstituted indolizidine (Daly, Spande, and Garraffo 2005); (i)5,6,8-trisubstituted indolizidine (Daly, Spande, and Garraffo 2005), (j) decahydroquinoline (Daly

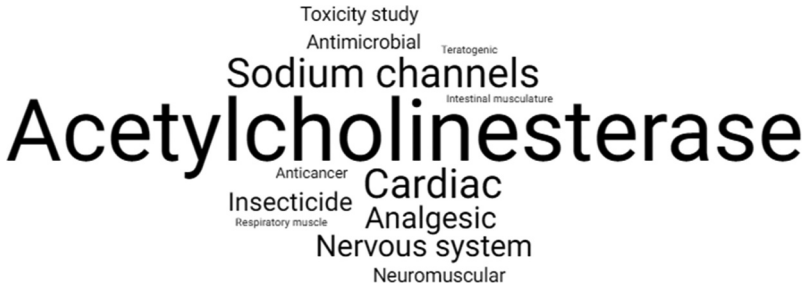


**Figure 4.** Word cloud with the sizing of the classes of biological activities tested experimentally from compounds of poisonous anurans of the family Dendrobatoidea year over 60 years.

adverse toxicity. Protti-Sánchez et al. (2019) determined the toxicity of batrachotoxin in *Phyllobates vittatus* (Cope, 1893) skin extracts obtained from three different localities using varying dilution patterns to assess toxicity patterns and found no lethality in mammals.

In *Epipedobates*, the main alkaloid cited was epibatidine ((−)-7-(3,4-dimethoxyphenyl)-1-methyl-6,7,8,9-tetrahydro-5 H-benzocyclohepten-5-ol), which has been widely studied and acts specifically on sodium channels with associated analgesic activity (Qian et al. 1993). Thus, *Epipedobates*-derived alkaloids also act as anticholinesterases (Qian et al. 1993), produce cardiorespiratory disturbances such as bradycardia and reduced respiratory rate (Fisher et al. 1994), impair muscular function (Green et al. 2018), and decrease fetal movement (Green et al. 2016, **2018**) activities. This compound was evaluated for development of (1) non-opioid analgesics, (2) nicotinic receptors, and (3) cardiac-lowering activity. In addition, epibatidine is a promising substance for medicinal bioprospecting (Dolci et al. 1999; Fox and Serrano 2007; Gotti et al. 2000; Houghtling, Dávila-García, and Kellar 1995; Khan, Yaksh, and Taylor 1997). Fitch et al. (2018) evaluated the activities of phantasmidine derived from *Epipedobates anthonyi* (Noble, 1921), which was tested for its potential for pharmaceutical use, and noted that the substance is a highly potent nicotinic receptor agonist. It is noteworthy that although it is found only in small amounts naturally, phantasmidine may be synthesized and exhibits actions similar to those of epibatidine, a widely studied alkaloid (Qian et al. 1993). Phantasmidine is extremely toxic and might result in respiratory failure. Consequently, this compound has a limited potential for pharmaceutical development, emphasizing the importance of handling this substance with caution during scientific investigations.

Mortari et al. (2004) identified pumiliotoxins in *Ameerega flavopicta* (Lutz, 1925) from samples obtained from the Brazilian cerrado. Pumiliotoxins comprise a class of alkaloids with pyrrolizidine or indolizidine rings, and histrionicotoxins, a class of alkaloids with a quinoline ring and an ethylamine side chain. In addition, decahydroquinoline was also detected. Bioassays of neurotoxic and myotoxic activities demonstrated significant biological activity. These effects were shown to be reversible upon withdrawal of contact with these alkaloids. These findings indicate complex and potent actions of these alkaloids on the nervous and muscular systems and suggest their potential therapeutic implications.

The importance of handling these compounds with caution should be emphasized because of their toxicity. For substances derived from *Oophaga pumilio* (Schmidt, 1857), Sheridan et al. (1991) showed that pumiliotoxins injected into the nerve cells of pigs, induced enhanced electrical activity in $Na^+$ channels. The action triggered spontaneous

**2005**), **223F** (Daly, Garraffo, and Spande 1993); (k) allopumiliotoxin (Daly, Garraffo, and Spande 1993); (l) homopumiliotoxin 207O (Daly, Spande, and Garraffo 2005); (m) 1, 4-disubstituted quinolizidine (Daly, Spande, and Garraffo 2005); (n) Tricyclic, precoccinelli, coccinelli (Daly et. al. **1993**), (o) Spiropyrrolizidine (Daly et. al. **2005**); (p) Piperidine (MacFoy et al. 2005); (q) pyrrolidine (MacFoy et al. 2005); (r) pseudophrynaminol (MacFoy et al. 2005); (s) 3,5-disubstituted pyrrolizidine (Daly, Garraffo, and Spande 1993); (t) lehmizidine (Protti-sánchez et. al, 2019); (u) Tretaponerine Macfoy et al (2005); (v) 3,5-disubstituted indolizidine (Daly, Spande, and Garraffo 2005).

and synchronous activity, with convulsions at regular frequencies without leading to dependence, due to the reduction of the minimum voltage for performance of the channel, without blocking inactivation, thus enhancing the performance in the channel closure stage by inversion (Sheridan et al. 1991). Thus, despite changing the action potentials to avoid depolarizing cells at rest, such as with batrachotoxin, spontaneous activity in neurones occurred. Hovey et al. (2018) and Mina et al. (2015) indicated that variations in alkaloid profiles, for ecological reasons, directly reflect their biological performance as antimicrobial agents, which was experimentally observed in both studies.

Frogs of the family Dendrobatidae contain a variety of highly potent and toxic alkaloids on their skin. The most prominent compounds are batrachotoxin, epibatidine, pumiliotoxins, histrionicotoxin, and decahydroquinoline. Batrachotoxin is known for its action as a sodium channel activator, initiating hyperexcitation of the nervous and muscular systems, leading to paralysis and subsequent death. In contrast, epibatidine acts as an agonist of the nicotinic acetylcholine receptors and exhibits extremely potent analgesic properties. Pumiliotoxins are complex alkaloids with pyrrolizidine or indolizidine rings, while histrionicotoxins comprise a class of alkaloids that contain a quinoline ring and an ethylamine side chain. Both compounds exhibit diverse biological activities, including ion channel inhibition. Further, decahydroquinoline has also been identified in frogs, indicating the richness and complexity of the alkaloids detected in these species. Understanding these compounds and their biological effects is of great interest in pharmacological research, but extreme caution is required in their handling and exposure owing to their significant toxicity (Daly et al. 2000, **2005**).

### *Referenced taxonomic groups*

Data demonstrated experiments examining biological activities of the substances extracted directly from the skin of anurans and the synthetic compounds (Table 1). However, all findings refer to the natural origin of chemical compounds presented in Table 1, which follow the citation of the family Dendrobatidae (11.87%), two (2) genera: *Phyllobates* (11.86%) and *Dendrobates* (1.69%), and 7 species. *Epipedobates tricolor* (Boulenger, 1899) presented the highest frequency of citations with 22.06%, followed by *Phyllobates aurotaenia* (Boulenger, 1913) with 16.95%, *Oophaga histrionica* (Berthold, 1845) and *Oophaga pumilio* with 11.86% each, *Phyllobates terribilis* with 1.69% (Myers, Daly & Malkin, 1978), *Epipedobates anthonyi* with 3.39% (Noble, 1921) and *Ameerega flavopicta* (Lutz, 1925) presented a single citation (1.69%). These 7 acknowledged species represent 4 distinct genera.

According to Grant and Frost (2016), there are at least 100 species of Dendrobatoidea that secrete toxic alkaloids; nevertheless, only the nomenclatures "Dendrobatidae," genus "*Phyllobates*," "*Dendrobates*" and seven species (*E. tricolor, P. aurotaenia, O. histrionica, O. pumilio, P. terribilis, E. anthonyi*, and *A. flavopicta*, which despite being inserted in the definitions, include groups with distinct genetic patterns for alkaloid tolerance. The designations of Dendrobatidae always refer to compounds present in the group (more broadly, as a family), but in this group, the type of secreted compound is not uniform and the profile of alkaloids differs between genera and populations of the same species.

The genus *Dendrobates*, despite being considered in older investigations, is synonymous with other genera. Few studies on *Dendrobates* with a single citation are available regarding the biological activity of their chemical compounds. The other reference genus, *Phyllobates*, is a physiological clade adapted for the secretion of highly toxic alkaloids such as batrachotoxin, one of the most lethal animal secretions, and has a low diversity of less toxic types, even when exposed to similar food patterns as that of sympatric species such as *O. pumilio*, *Dendrobates auratus* (Girard, 1855), and *Oophaga granulifera* (Taylor, 1958) (Castano et al. 2009; Mebs et al. 2014).

An essential aspect to consider is that within Dendrobatoidea, variations exist in the compounds secreted by populations from different localities. Bolton et al. (2017) noted that the alkaloids secreted by Dendrobatidae depend upon the palatability pattern of arthropods; that is, these compounds are influenced by the available diet,

**Table 1.** Biological activity studies of compounds originating from Dendrobatoidea anurans.

| Biological activity studies | Class of alkaloids/ derivatives | Alkaloid subclass | Type of bioassay | Obtaining the alkaloid | Species or group cited | Reference |
|---|---|---|---|---|---|---|
| Acetylcholinesterase | batrachotoxin (a)<br>pumiliotoxin (b)<br>gephyrotoxin (c) | batrachotoxin<br>**323A** | *in vivo* | synthesis, isolation | Dendrobatidae | Mensah-Dwumah and Daly, (1968) |
| | pyridinic (d) | epibatidine | *in vivo* | synthesis | *Epipedobates tricolor* | Shimizu and Yokotani, (2009) |
| | | | *in vivo, in vitro* | synthesis | | Rupniak et al., (1994) |
| | | | *in vivo* | synthesis | | Dolci et al., (1999) |
| | | | *in vivo* | synthesis | | Alkondon and Albuquerque, (1995) |
| | | | *in vivo, in vitro* | synthesis | | Houghtling et al., (1995) |
| | | | *in vivo, in vitro* | synthesis | | Heugebaert et al., (2014) |
| | | | *in vivo* | synthesis | | Khan et al., (1997) |
| | | | *in vivo* | synthesis | *Epipedobates tricolor* | Fisher et al., (1994) |
| | epiquinamide (e) | | *in vitro* | isolation | | Fitch et al., (2003) |
| | pyridinic (d) | phantasmidine | *in vitro* | isolation | *Epipedobates anthonyi* | Fitch et al., (2010) |
| | | | *in vivo, in vitro, in silico* | synthesis | | Fitch et al., (2018) |
| | histrionicotoxin (f) | perhistrionicotoxin derived from **285A** | *in vivo* | isolation | *Oophaga histrionica* | Eldefrawi et al., (1977) |
| | | **283A, 285A** | *in vivo* | isolation | | Daly et al., (1971) |
| | | **283A, 285E** | *in vivo* | isolation | | Kato et al., (1975) |
| | | **285A** | *in silico* | isolation | | Karle, (1973) |
| | | perhistrionicotoxin derived from **285A** | *in vivo* | isolation | | Albuquerque et al., (1973) |
| Analgesic | pyridinic (d) | epibatidine | *in vivo* | synthesis | *Epipedobates tricolor* | Qian et al., (1993) |
| | | | *in vivo, in vitro* | synthesis | | Rupniak et al., (1994) |
| | batrachotoxin (a) | batrachotoxin | *in vivo* | synthesis | | Bosmans et al., (2004) |
| | | | *in vitro, in silico* | synthesis | *Phyllobates* | Toma et al., (2016) |
| | | | *in vitro* | isolation | *Phyllobates aurotaenia* | Adams et al., (1978) |
| Anticancer | indolizine (g) | | *in vitro* | synthesis | *Dendrobates* | Sandeep et al., (2016) |
| | batrachotoxin (a) | batrachotoxin | *in vitro* | isolation | *Phyllobates aurotaenia* | Catterall, (1975) |
| Antimicrobial | 5,8-disubstituted indolizidine (h)<br>5,6,8-trisubstituted indolizidine (i)<br>decahydroquinoline (j)<br>histrionicotoxin (f) | | *in vitro* | isolation | *Oophaga pumilio* | Hovey et al., (2018) |

(*Continued*)

**Table 1.** (Continued).

| Biological activity studies | Class of alkaloids/ derivatives | Alkaloid subclass | Type of bioassay | Obtaining the alkaloid | Species or group cited | Reference |
|---|---|---|---|---|---|---|
| | 5,8-disubstituted indolizidine (h) | **205A, 207A, 237D, 247E, 249O, 251N, 259B, 209S, 235B, 257C 251T, 253 H, 265 V, 265 L, 231B, 249C, 251 M, 259C, 263A, 237C, 223A, 223X** | *in vitro* | isolation | | Mina et al., (2015) |
| | 5,6,8-trisubstituted indolizidine (i) | **251D, 323A, 323F, 307A, 309C, 323B** | | | | |
| | | **267A, 341A, 323B** | | | | |
| | pumiliotoxin (b) | deoxyhomopumiliotoxin **207O** | | | | |
| | allopumiliotoxin (k) | **257D** | | | | |
| | homopumiliotoxin (l), | **205 H, 207J, 235I, 253 G** | | | | |
| | 1, 4-disubstituted quinolizidine (m) | **252A** | | | | |
| | | **213A, 241D, 225B** | | | | |
| | tricyclic (n) | **277D, 225C** | | | | |
| | spiropyrrolizidine (o) | **223B, 223 H, 251K** | | | | |
| | piperidine (p) | **195A, 211A, 269A, 269B, 269AB, 275B, 271D, 223F** | | | | |
| | pyrrolidine (q) | **275A** | | | | |
| | 3,5-disubstituted pyrrolizidine (r) | **283A, 285A, 287A, 287B** | | | | |
| | | **207F, 235S, 249N, 207N** | | | | |
| | decahydroquinoline (j) | | | | | |
| | lehmizidine (s) | | | | | |
| | histrionicotoxin (f) | | | | | |
| | unclassified | | | | | |
| | pyrrolidine (q) | (*cis/trans* $R^1$= n-$C_7H_{15}$, $R^2$= n-$C_6H_{13}$; $R^3$=H), (*cis/trans* $R^1$= $C_2H_5$, $R^2$= n-$C_{13}H_{27}$; $R^3$= | *in vitro* | synthesis, isolation | Dendrobatidae | Macfoy et al., (2005) |
| | piperidine (p) | H), (*cis/trans* $R^1$= $R^2$= n-$C_5H_{11}$, $R^3$= $CH_3$) | | | | |
| | pyridinic (d) | ($R^1$= H, $R^2$= n-$C_9H_{19}$), (*cis/trans* $R^1$= $CH_3$, $R^2$= n-$C_{11}H_{23}$), (*trans* $R^1$= $CH_3$, $R^2$= | | | | |
| | decahydroquinoline (j) | n-$C_{15}H_{31}$), (*cis* $R^1$= $CH_3$, $R^2$= $(CH_2)_2CHOHCH_2CH_3$) | | | | |
| | indolizidine (g) | (*R*= n-$C_{11}H_{23}$), (*R*= $CH_2CHOH(CH_2)_8CH_3$) | | | | |
| | histrionicotoxin (f) | **223F**, **243A**, (2 R,5S)-Decahydro-2-(5-methoxypentyl)-5-methylquinoline, | | | | |
| | pumiliotoxin (b) | ($R^1$= $R^2$= n-$C_4H_9$ $R^3$=H), **239AB, 235B,'** | | | | |
| | pseudophrynaminol (t) | ($R^1$= n-$C_4H_9$, $R^2$= n-$C_5H_{91}$), ($R^1$= n-$C_3H_7$, $R^2$= H) | | | | |
| | spiropyrrolizidine (o) | **251D**, ($R^1$= n-$C_6H_{13}$, $R^2$= H), **307A**. | | | | |
| | tetraponerine (u) | pseudophrynaminol | | | | |
| | batrachotoxin (a) | **236** | | | | |
| | | tetraponerine I | | | | |
| | | batrachotoxin A (R=H), batrachotoxin | | | | |
| Cardiac | batrachotoxin (a) | batrachotoxin | *in vivo* | isolation | *Phyllobates aurotaenia* | Kayaalp et al., (1970) |
| | | | *in vitro* | isolation | | Roseen J S and Fuhrman F A, (1971) |
| | | | *in vivo* | synthesis | | Honerjager and Reiter, (1977) |
| | batrachotoxin (a) | batrachotoxin | *in vivo* | synthesis | Dendrobatidae | Mensah-Dwumah and Daly, (1968) |
| | pumiliotoxin (b) | **323A** | | | | |
| | pyridinic (d) | epibatidine | *in vivo* | synthesis | *Epipedobates tricolor* | Khan et al., (1997) |
| | pumiliotoxin (b) | **323A** | *in vivo* | isolation | *Oophaga pumilio* | Daly et al., (1985) |
| | batrachotoxin (a) | batrachotoxin A | *in vivo*, | isolation | *Phyllobates* | Protti-Sánchez et al., (2019) |
| | decahydroquinoline (j) | **251A** | *in silico* | | | |
| | lehmizidine (s) | **275A** | | | | |
| | pyridinic (d) | epibatidine | *in vivo* | synthesis | *Epipedobates tricolor* | Fisher et al., (1994) |

(*Continued*)

**Table 1.** (Continued).

| Biological activity studies | Class of alkaloids/ derivatives | Alkaloid subclass | Type of bioassay | Obtaining the alkaloid | Species or group cited | Reference |
|---|---|---|---|---|---|---|
| Neuromuscular | batrachotoxin (a) | batrachotoxin | *in vivo* | isolation | *Phyllobates aurotaenia* | Daly et al., (1972) |
| | histrionicotoxin (f) | **283A**, (perhistrionicotoxin derived from **285A**) | *in vitro* | isolation | *Oophaga histrionica* | Lapa et al., (1975) |
| | histrionicotoxin (f) | **283A** | *in vitro* | isolation | *Oophaga histrionica* | Masukawa and Albuquerque, (1978) |
| | pumiliotoxin (b) | **323A** | *in vivo* | isolation | *Oophaga pumilio* | D'Este et al., (1999) |
| Respiratory muscle | batrachotoxin (a) | batrachotoxin | *in vivo* | synthesis | Dendrobatidae | Mensah-Dwumah and Daly, (1968) |
| | histrionicotoxin (f) | **285A** | | | | |
| | pumiliotoxin (b) | **323A** | | | | |
| | pyridinic (d) | epibatidine | *in vivo* | synthesis | *Epipedobates tricolor* | Fisher et al., (1994) |
| Intestinal musculature | batrachotoxin (a), pumiliotoxin (b) | batrachotoxin **323A** | *in vivo* | synthesis | Dendrobatidae | Mensah-Dwumah and Daly, (1968) |
| Nervous system | batrachotoxin (a) | batrachotoxin | *in vitro* | isolation | *Phyllobates aurotaenia* | Narahashi and Deguchi, (1970) |
| | | | *in vivo* | isolation | | Kayaalp et al., (1970) |
| | pyridinic (d) | epibatidine | *in vivo* | synthesis | | Khan et al., (1997) |
| | pumiliotoxin (b) | **323A** | *in vivo* | isolation | *Oophaga pumilio* | D'Este et al., (1999) |
| | | | *in vitro* | isolation | | Sheridan et al., (1991) |
| Sodium channels | batrachotoxin (a) | batrachotoxin | *in vitro* | isolation | *Phyllobates* | Li et al., (2002) |
| | | | *in vitro* | isolation | *Phyllobates aurotaenia* | Huang et al., (1979) |
| | | | *in vitro* | isolation | *Phyllobates terribilis* | Wang and Wang, (2017) |
| | | | *in vitro, in silico* | synthesis | *Phyllobates* | Toma et al., (2016) |
| | | | *in vitro* | isolation | | Linford et al., (1998) |
| | batrachotoxin (a) | batrachotoxin | *in vivo* | synthesis | | Gusovsky et al., (1986) |
| | pumiliotoxin (b) | **323A** | | | | |
| | pumiliotoxin (b) | **323A** | *in vitro* | isolation | *Oophaga pumilio* | Sheridan et al., (1991) |
| Toxicity study | batrachotoxin (a) | batrachotoxin A | *in vivo, in silico* | isolation | *Phyllobates* | Protti-Sánchez et al., (2019) |
| | decahydroquinoline | **251A** | | | | |
| | lehmizidine (s) | **275A** | | | | |
| | pumiliotoxin (b) | **251D** | *in vivo, in vitro* | isolation | *Ameerega flavopicta* | Mortari et al., (2004) |
| | histrionicotoxin (f) | **285A** | | | | |
| | decahydroquinoline (j) | **219A, 243A** | | | | |
| | pumiliotoxin (b) | **251D** | *in vitro* | synthesis | Dendrobatidae | Vandendriessche et al., (2008) |

(*Continued*)

**Table 1.** (Continued).

| Biological activity studies | Class of alkaloids/ derivatives | Alkaloid subclass | Type of bioassay | Obtaining the alkaloid | Species or group cited | Reference |
|---|---|---|---|---|---|---|
| Insecticide | batrachotoxin (a)<br>pumiliotoxin (b)<br>allopumiliotoxin (k)<br>decahydroquinoline (j)<br>pseudophrynaminol (t)<br>spiropyrrolizidine (o)<br>gephyrotoxin (c)<br>5,8-disubstituted indolizidine (h)<br>3,5-disubstituted indolizidine (v)<br>pyridinic (d)<br>histrionicotoxin (f)<br>piperidine (p) | batrachotoxin A, batrachotoxinin<br>**237A, 267C**, **251D**, **307A, 323A**<br>**267A**<br>*cis*-**223F**<br>**205A, 235B**<br>**223AB**<br>nicotine<br>**259A, 285A, 291A**<br>2-Methyl-6-undecylpiperidine | *in vivo* | isolation, synthesis | Dendrobatidae | Weldon et al., (2013) |
| | pumiliotoxin (b) | **251D** | *in vivo*<br>*in vitro* | synthesis<br>synthesis | | Weldon et al., (2006)<br>Vandendriessche et al., (2008) |
| | | | *in vivo* | synthesis | *Oophaga pumilio* | Bargar et al., (1995) |
| Teratogenic | pyridinic (d) | epibatidine | *in vivo* | isolation | *Epipedobates tricolor* | Green et al., (2018) |

which varies between specialist or generalist species and environmental conditions. Consequently, it becomes evident that research concerning this group of Dendrobatoidea needs to be broadened in scope to encompass a larger number of species and diverse regions for comprehensive analyses. In the species cited, there are several studies on chemical ecology, for example, Saporito et al. (2007) studied the evaluation of *Oophaga pumilio* alkaloids in Panama over a period of 30 years.

Dendrobatoidea is a group distributed in Nicaragua to the Pacific slopes of Colombia and Ecuador, east of the Andes to Bolivia, and to Guianas and southeastern Brazil. However, most of the species referenced with bioactive agents are of Andean or Western Amazon distribution, with only *Epipedobates flavopictus* cited from Brazil, which is related to the Cerrado ecosystem. These aspects indicate the need for expansion of studies on species with greater distribution and endemic distribution in the Eastern Amazon.

According to Ferreira et al. (2023), the use of natural products from animal sources must be considered fundamental from a social and economic perspective for Brazil's scientific and commercial progress, given its rich biodiversity. Recognizing biodiversity and its natural products as a pharmaceutical library makes it possible to scale sustainable guarantees for the bioeconomic chain, in which biotechnological production generates goods that improve the quality of life of societies in a sustainable manner by adding value to natural capital while protecting natural resources (Astolfi-Filho, Silva, and Bigi 2014).

### *Data analysis and infographics*

The representative word clouds integrated into this study were meticulously designed to generate a visually comprehensible representation that precisely encompassed the key molecules or categories of alkaloids that were isolated and identified in the scientifically reviewed studies of the systematic review. Special attention was directed toward decahydroquinoline, as well as the classes of alkaloids batrachotoxin, pumiliotoxin, and histrionicotoxin, along with their biological activities that interact with the enzyme acetylcholinesterase and their effects within the neuromuscular and analgesic domains (Wang et al. 2020).

It is of critical importance to emphasize that the preference for *in vitro* methods, notably assays involving the inhibition of acetylcholinesterase activity, has led to an increased emphasis on these tests owing to their economic feasibility and viability of their implementation in spectrophotometry systems. These tests offer easy reproducibility and repeatability even when performed by less experienced analysts. It is important to emphasize not undermining the legitimacy of the responses generated through these *in vitro* methods, but rather to indicate the need for a comprehensive evaluation of manifestations related to neuromuscular activities in *in vivo* systems. Notably, absent from the studies reviewed were *in silico* methods; however, these methods are evidently gaining traction as these assays enable the screening of molecules, pharmacophores, and simulations of biological and toxicological activities (Liu, Xu, and Dong 2021; Marucci et al. 2021).

These alkaloids play critical roles in ecosystems and have been the subject of extensive research owing to their significant biological activities. Through these analyses, it is possible to elucidate connections that transcend the boundaries of individual molecules, offering comprehensive perspectives on their interactions with biological systems. Further, by exploring alkaloids originating from animals, a promising avenue emerges for determining the intricate evolutionary adaptations that led to the synthesis, transformation, or accumulation of these compounds in specific ecological contexts. This understanding not only expands our perception of chemical diversity but also enhances potential paths for biomedical and pharmaceutical applications (Islam and Mubarak 2020; Zhang et al. 2020).

## Conclusions

An analysis of the reference scientific literature showed that the biological activities of compounds existing in the venom of Dendrobatoidea anurans are not well understood and research has been

published in relatively few articles, despite their potential for bioprospective analysis of drugs. Of the few species referenced in the research, there is a lack of comprehensive studies on animals of the Eastern Amazon; therefore, it is necessary to encourage investigations on other species and in different populations to expand the library of chemical compounds.

Studies on potential biological compounds are centered on established compounds, such as batrachotoxin, epibatine, pumiliotoxin, and histrionicotoxin, although indolizidine, quinolizidine, pyrrolidine, and gephyrotoxin, are significantly less cited as potential pharmacological agents. *In vivo* tests were used to assess the neuromuscular activity, respiratory muscles, and intestinal musculature. However, despite the numerous benefits and vast chemical libraries of silicon testing, *in silico* tests are largely lacking.

The biological activities of anuran alkaloids include: 1) inhibition of acetylcholinesterase, cardiac tissue and intestinal musculature (2) as an analgesic, antineoplastic, antimicrobial and insecticide, 3) actions on the central and peripheral nervous system, neuromuscular system, and respiratory muscle, 4) effects on sodium channels, 4) teratogenicity, and 5) general toxicity. Batrachotoxin exhibited most of the activities considered in this study, but its pharmacological use is restricted in its natural form because it is a highly toxic compound. Similarly, phantasmidine exhibits a high degree of toxicity. The alkaloid of the pyridinic class, epibatina, acts as an agonist of nicotinic acetylcholine receptors, exhibiting extremely potent reversible analgesic properties and therefore has vast medicinal potential.

These findings indicate the diverse and potent bioactive properties of the alkaloids present in Dendrobatidae anurans, displaying high potential for bioprospective and pharmacological applications. Thus, the recognition of these bioactive compounds represents a scientific advancement and may act as a marker of environmental importance by defining biodiversity as natural capital and as a reserve for use in the future, which urgently needs to be protected. Similarly, the potential for biotechnological and pharmacological use of genetic heritage, if managed, might generate benefits for humanity, such as the development of medicines to counteract various diseases and for other purposes.

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## References

Abookleesh, F. L., B. S. Al-Anzi, and A. Ullah. 2022. "Potential Antiviral Action of Alkaloids." *Molecules* 27 (3): 903. https://doi.org/10.3390/molecules27030903.

Acunha, T., B. A. Rocha, V. Nardini, F. Barbosa-Júnior, and L. H. Faccioli. 2023. "Lipidomic Profiling of the Brazilian Yellow Scorpion Venom: New Insights into Inflammatory Responses Following *Tityus Serrulatus* Envenomation." *Journal of Toxicology and Environmental Health Part A* 86 (9): 283–295. https://doi.org/10.1080/15287394.2023.2188896.

Adams, H. J., A. R. Mastri, D. Doherty, and D. Charron. 1978. "Spinal Anesthesia with Batrachotoxin in Sheep and Microscopic Examination of Spinal Cords and Roots." *Pharmacological Research Communications* 10 (8): 719–728. https://doi.org/10.1016/S0031-6989(78)80041-1.

Ajebli, M., H. Khan, and M. Eddouks. 2021. "Natural Alkaloids and Diabetes Mellitus: A Review." *Endocr Metab Immune Disorder Drug Target* 21 (1): 111–130. https://doi.org/10.2174/1871530320666200821124817.

Albuquerque, E., E. A. Barnardt, T. H. Chiut, A. J. Lapa, J. Oliver, S. E. Jansson, J. Daly, and B. Witkop. 1973. "Acetylcholine Receptor and Ion Conductance Modulator Sites at the Murine Neuromuscular Junction: Evidence from Specific Toxin Reactions." *Proceedings of the National Academy of Sciences of the United States of America* 70 (3): 949–953. https://doi.org/10.1073/pnas.70.3.949.

Alkondon, M., and E. Albuquerque. 1995. "Diversity of Nicotinic Acetylcholine Receptors in Rat Hippocampal Neurons. III. Agonist Actions of the Novel Alkaloid Epibatidine and Analysis of Type II Current." *The Journal of Pharmacology and Experimental Therapeutics* 274 (2): 771–782. ISSN 0022-3565, PubMed 8510022.

Astolfi-Filho, S., C. G. N. S. Silva, and M. F. M. A. Bigi. 2014. "Bioprospecção e biotecnologia." *Parcerias Estratégicas* 19:45–80. https://seer.cgee.org.br/parcerias_estrategicas/issue/view/75.

Atanasov, A. G., S. B. Zotchev, and V. M. Dirsch, C. T. Supuran. 2021. "The International Natural Product Sciences Taskforce." *Natural Products in Drug Discovery Advances and Opportunities Nat Rev Drud Discov* 20 (3): 200–216. https://doi.org/10.1038/s41573-020-00114-z.

Bargar, T. M., R. M. Lett, P. L. Johnson, J. E. Hunter, C. P. Chang, D. J. Pernich, M. R. Sabol, and M. R. Dick. 1995. "Toxicity of Pumiliotoxin 251D and Synthetic Analogs to the Cotton Pest *Heliothis Virescens*." *Journal of Agricultural and Food Chemistry* 43 (4): 1044–1051. https://doi.org/10.1021/jf00052a037.

Barreiro, E. J., and V. S. Bolzani. 2009. "Biodiversidade: fonte potencial para a descoberta de fármacos." *Quimica nova* 32 (3): 679–688. https://doi.org/10.1590/S0100-40422009000300012.

Barros, A. L. A. N., A. Hamed, M. Marani, D. C. Moreira, P. Eaton, A. Plácido, M. J. Kato, and J. R. S. A. Leite. 2022. "The Arsenal of Bioactive Molecules in the Skin Secretion of Urodele Amphibians." *Frontiers in Pharmacology* 12:1–7. https://doi.org/10.3389/fphar.2021.810821.

Basham, E. W., R. A. Saporito, M. González-Pinzón, A. Romero-Marcucci, and B. R. Scheffers. 2021. "Chemical Defenses Shift with the Seasonal Vertical Migration of a Panamanian Poison Frog." *Biotropica* 53 (1): 28–37. https://doi.org/10.1111/btp.12842.

Bauer, A., and M. Bronstrup. 2014. "Industrial Natural Product Chemistry for Drug Discovery and Development." *Natural Product Reports* 31 (1): 35–60. https://doi.org/10.1039/c3np70058e.

Bolton, S. K., K. Dickerson, and R. A. Saporito. 2017. "Variable Alkaloid Defenses in the Dendrobatid Poison Frog *Oophaga Pumilio* are Perceived as Differences in Palatability to Arthropods." *Journal of Chemical Ecology* 43 (3): 273–289. https://doi.org/10.1007/s10886-017-0827-y.

Bordon, K. C. F., C. T. Cologna, E. C. Fornari-Baldo, E. L. Pinheiro-Júnior, F. A. Cerni, F. G. Amorim, F. A. P. Anjolette, et al. 2020. "From Animal Poisons and Venoms to Medicines: Achievements, Challenges and Perspectives in Drug Discovery." *Frontiers in Pharmacology* 11:1132. https://doi.org/10.3389/fphar.2020.01132.

Bosmans, F., C. Maertens, F. Verdonck, and J. Tytgat. 2004. "The Poison Dart Frog's Batrachotoxin Modulates Na V 1.8." *FEBS Letters* 577 (1–2): 245–248. https://doi.org/10.1016/j.febslet.2004.10.017.

Brands, S. J. 2022. *The Taxonomicon. (Ed.), 2022. Universal Taxonomic Services, Zwaag, the Netherlands*. http://taxonomicon.taxonomy.nl/]. Access date: 30 aug. [http://taxonomicon.taxonomy.nl/]. Access date. 30 aug. 2023.

Castano, S., L. Frezza, A. Labro, L. Fierro, F. Bezanilla, A. M. Correa, B. D. Holzherr, K. Jurkat-Rott, A. K. Alekov, and F. Lehmann-Horn. 2009. "Cloning and Sequence Analysis of the Voltage-Gated Muscle Na+ Channel from the Poison Dart Frog *Phyllobates Aurotaenia*." *Biophysical Journal* 96 (3): 247a. https://doi.org/10.1016/j.bpj.2008.12.1214.

Catterall, W. A. 1975. "Activation of the Action Potential Na+ Ionophore of Cultured Neuroblastoma Cells by Veratridine and Batrachotoxin." *The Journal of Biological Chemistry* 250 (11): 4053–4059. https://doi.org/10.1016/s0021-9258(19)41385-9.

Caty, S. N., A. Alvarez-Buylla, G. D. Byrd, C. Vidoudez, A. B. Roland, E. E. Tapia, B. Budnik, S. A. Trauger, L. A. Coloma, and L. A. O'Connell. 2019. "Molecular Physiology of Chemical Defenses in a Poison Frog." *The Journal of Experimental Biology* 222:1–12. https://doi.org/10.1242/jeb.204149.

Cely-Veloza, W., M. J. Kato, and E. Coy-Barrera. 2023. "Quinolizidine-Type Alkaloids: Chemodiversity, Occurrence, and Bioactivity." *ACS Omega* 8 (31): 27862–27893. https://doi.org/10.1021/acsomega.3c02179.

Chen, N., S. Xu, Y. Zhang, and F. Wang. 2018. "Animal Protein Toxins: Origins and Therapeutic Applications." *Biophysics Reports* 4 (5): 233–242. https://doi.org/10.1007/s41048-018-0067-x.

Cordell, G. A., M. L. Quinn-Beattie, and N. R. Farnsworth. 2001. "The Potential of Alkaloids in Drug Discovery." *Phytotherapy Research: PTR* 15 (3): 183–205. https://doi.org/10.1002/ptr.890.

Daly, J. W. 1982. "Biologically Active Alkaloids from Poison Frogs (Dendrobatidae)." *Journal of Toxicology Toxin Reviews* 1 (1): 33–86. https://doi.org/10.3109/15569548209016467.

Daly, J. W., E. X. Albuquerque, F. C. Kauffman, and F. Oesch. 1972. "EFFECTS of BACTRACHOTOXIN on ELECTROPLAX Na + -K + -ATPase and LEVELS of ATP in RAT MUSCLE." *Journal of Neurochemistry* 19 (12): 2829–2833. https://doi.org/10.1111/j.1471-4159.1972.tb03820.x.

Daly, J. W., H. M. Garraffo, and T. F. Spande. 1993. "Amphibian Alkaloids." *The Alkaloids: Chemistry and Pharmacology*, 185–288. Academic Press 43.

Daly, J. W., H. M. Garraffo, T. F. Spande, M. W. Decker, J. P. Sullivan, and M. Williams. 2000. "Alkaloids from Frog Skin: The Discovery of Epibatidine and the Potential for

Developing Novel Non-Opioid Analgesics." *Natural Product Reports* 17 (2): 131–135. https://doi.org/10.1039/a900728h.

Daly, J. W., I. Karlet, C. W. Myers, T. T. Ma, J. A. Waters, and B. Witkop. 1971. "Histrionicotoxins: Roentgen-Ray Analysis of the Novel Allenic and Acetylenic Spiroalkaloids Isolated from a Colombian Frog, *Dendrobates Histrionicus*." *Proceedings of the National Academy of Sciences of the United States of America* 68 (8): 1870–1875. https://doi.org/10.1073/pnas.68.8.187.

Daly, J. W., E. T. McNeal, L. E. Overman, and D. H. Ellison. 1985. "A New Class of Cardiotonic Agents: Structure-Activity Correlations for Natural and Synthetic Analogues of the Alkaloid Pumiliotoxin B (8-Hydroxy-8-Methyl-6-Alkylidene-1-Azabicyclo[4.3.0]nonanes)." *Journal of Medicinal Chemistry* 28 (4): 482–486. https://doi.org/10.1021/jm00382a017.

Daly, J. W., and C. W. Myers. 1967. "Toxicity of Panamanian Poison Frogs (*Dendrobates*): Some Biological and Chemical Aspects." *Science* 156 (3777): 970–973. https://doi.org/10.1126/science.156.3777.970.

Daly, J. W., T. F. Spande, and H. M. Garraffo. 2005. "Alkaloids from Amphibian Skin: A Tabulation of Over Eight-Hundred Compounds." *Journal of Natural Products* 68 (10): 1556–1575. https://doi.org/10.1021/np0580560.

D'Este, L., G. Falconieri-Erspamer, C. Severini, V. Erspamer, and T. G. Renda. 1999. "Neuropeptide Y Release by Pumiliotoxin-B in the Electrically-Stimulated Mouse Vas Deferens: An Immunohistochemical Study." *Peptides* 20 (7): 809–816. https://doi.org/10.1016/S0196-9781(99)00066-2.

Dolci, L., F. Dolle, H. Valette, F. Vaufrey, C. Fuseau, M. Bottlaender, and C. Crouzel. 1999. "Synthesis of a Fluorine-18 Labeled Derivative of Epibatidine for *In Vivo* Nicotinic Acetylcholine Receptor PET Imaging." *Bioorganic & Medicinal Chemistry* 7 (3): 467–479. https://doi.org/10.1016/S0968-0896(98)00261-2.

Eldefrawi, A. T., M. E. Eldefrawi, E. X. Albuquerque, A. C. Oliveira, N. Mansour, M. Adler, J. W. Daly, G. B. Brown, W. Burgermeister, and B. Witkop. 1977. "Perhydrohistrionicotoxin: A Potential Ligand for the Ion Conductance Modulator of the Acetylcholine Receptor." *Proceedings of the National Academy of Sciences of the United States of America* 74 (5): 2172–2176. https://doi.org/10.1073/pnas.74.5.2172.

Ferreira, P. M. P., D. D. R. Arcanjo, and A. P. Peron. 2023. "Drug Development, Brazilian Biodiversity and Political Choices: Where are We Heading?" *Journal of Toxicology and Environmental Health - Part B* 26 (5): 257–274. https://doi.org/10.1080/10937404.2023.2193762.

Fisher, M., D. Huangfu, T. Y. Shen, and P. G. Guyenet. 1994. "Epibatidine, an Alkaloid from the Poison Frog *Epipedobates tricolor*, is a Powerful Ganglionic Depolarizing Agent." *The Journal of Pharmacology and Experimental Therapeutics* 270 (2): 702–707. ISSN 0022-3565, PubMed 8071862.

Fitch, R. W., H. M. Garraffo, T. F. Spande, H. J. C. Yeh, and J. W. Daly. 2003. "Bioassay-Guided Isolation of Epiquinamide, a Novel Quinolizidine Alkaloid and Nicotinic Agonist from an Ecuadoran Poison Frog, *Epipedobates Tricolor*." *Journal of Natural Products* 66 (10): 1345–1350. https://doi.org/10.1021/np030306u.

Fitch, R. W., B. B. Snider, Q. Zhou, B. M. Foxman, A. A. Pandya, J. L. Yakel, T. T. Olson, et al. 2018. "Absolute Configuration and Pharmacology of the Poison Frog Alkaloid Phantasmidine." *Journal of Natural Products* 81 (4): 1029–1035. https://doi.org/10.1021/acs.jnatprod.8b00062.

Fitch, R. W., T. F. Spande, H. M. Garraffo, H. J. C. Yeh, and J. W. Daly. 2010. "Phantasmidine: An Epibatidine Congener from the Ecuadorian Poison Frog *Epipedobates Anthonyi*." *Journal of Natural Products* 73:331–337. https://doi.org/10.1021/np900727e.

Fox, J. W., and S. M. T. Serrano. 2007. "Approaching the Golden Age of Natural Product Pharmaceuticals from Venom Libraries: An Overview of Toxins and Toxin-Derivatives Currently Involved in Therapeutic or Diagnostic Applications." *Current Pharmaceutical Design* 13 (28): 2927–2934. https://doi.org/10.2174/138161207782023739.

Furtado, R. A., S. D. Ozelin, N. H. Ferreira, B. A. Miura, S. Almeida, G. M. Magalhaes, E. J. Nassar, M. A. Miranda, J. K. Bastos, and D. D. Tavares. 2022. "Antitumor Activity of Solamargine in Mouse Melanoma Model: Relevance to Clinical Safety." *Journal of Toxicology & Environmental Health A* 85 (4): 131–142. https://doi.org/10.1080/15287394.2021.1984348.

Gonzalez, M., P. Palacios-Rodriguez, J. Hernandez-Restrepo, M. González-Santoro, A. Amézquita, A. E. Brunetti, and C. Carazzone. 2021. "First Characterization of Toxic Alkaloids and Volatile Organic Compounds (VOCs) in the Cryptic Dendrobatid *Silverstoneia Punctiventris*." *Frontiers in Zoology* 18 (1): 1–15. https://doi.org/10.1186/s12983-021-00420-1.

Gotti, C., E. Carbonnelle, M. Moretti, R. Zwart, and F. Clementi. 2000. "Drugs Selective for Nicotinic Receptor Subtypes: A Real Possibility or a Dream?" *Behavioural Brain Research* 113 (1–2): 183–192. https://doi.org/10.1016/S0166-4328(00)00212-6.

Grant, T., and D. R. Frost. 2016. "Recent Progress in the Systematics of Poison Frogs and Their Relatives (Dendrobatoidea)." In In *Aposematic Poison Frogs (Dendrobatidae) of the Andean Countries: Bolivia, Colombia, Ecuador, Perú and Venezuela. In Conservation International*, edited by T. R. Kahn, L. A. Marca, L. S, J. L. Brown, E. Twomey, and A. Amézquita, 9–18 2016.

Green, B. T., S. T. Lee, J. W. Keele, K. D. Welch, D. Cook, J. A. Pfister, and W. R. Kem. 2018. "Complete Inhibition of Fetal Movement in the Day 40 Pregnant Goat Model by the Piperidine Alkaloid Anabasine but Not Related Alkaloids." *Toxicon* 144:61–67. https://doi.org/10.1016/j.toxicon.2018.02.007.

Green, B. T., S. T. Lee, K. D. Welch, D. Cook, and W. R. Kem. 2016. "Activation and Desensitization of Peripheral Muscle and Neuronal Nicotinic Acetylcholine Receptors by Selected, Naturally-Occurring Pyridine Alkaloids." *Toxins* 8 (7): 1–12. https://doi.org/10.3390/toxins8070204.

Gusovsky, F., E. B. Hollingsworth, J. W. Daly, and G. Brown. 1986. "Regulation of Phosphatidylinositol Turnover in Brain Synaptoneurosomes: Stimulatory Effects of Agents That Enhance Influx of Sodium Ions (Inositol Phosphates/Pumiliotoxin/Batrachotoxin/Tetrodotoxin/ Saidtoxin)." *Proceedings of the National Academy of Sciences of the United States of America* 83 (9): 3003–3007. https://doi.org/10.1073/pnas.83.9.3003.

Gutiérrez, K., R. Morales, and J. Pino. 2018. "Ranas dardo venenosas (Dendrobatidae) y su importancia en la bioprospección de moléculas bioactivas en los últimos tiempos: una revisión poison dart frog (Dendrobatidae) and their." *Revista de Iniciación Científica - Edición Especial* 4:43–47. https://doi.org/10.33412/rev-ric.v4.0.1818.

Heugebaert, T. S. A., M. Van Overtveldt, A. Blieck, B. Wuyts, P. Augustijns, E. Ponce-Gámez, A. Rivera, et al. 2014. "Synthesis of 1-Substituted Epibatidine Analogues and Their *In Vitro* and *In Vivo* Evaluation as α4β2 Nicotinic Acetylcholine Receptor Ligands." *Royal Society of Chemistry Advances Journal* 4 (5): 2226–2234. https://doi.org/10.1039/c3ra44379e.

Honerjager, P., and M. Reiter. 1977. "The Cardiotoxic Effect of Batrachotoxin." *Naunyn-Schmiedeberg's Archives of Pharmacology* 299 (3): 239–252. https://doi.org/10.1007/BF00500316.

Houghtling, R. A., M. I. Dávila-García, and K. J. Kellar. 1995. "Characterization of (±)-[3H] Epibatidine Binding to Nicotinic Cholinergic Receptors in Rat and Human Brain." *Molecular Pharmacology* 48:280–287.

Hovey, K. J., E. M. Seiter, E. E. Johnson, and R. A. Saporito. 2018. "Sequestered Alkaloid Defenses in the Dendrobatid Poison Frog *Oophaga Pumilio* Provide Variable Protection from Microbial Pathogens." *Journal of Chemical Ecology* 44 (3): 312–325. https://doi.org/10.1007/s10886-018-0930-8.

Huang, L.-Y. M., W. A. Catterall, and G. Ehrenstein. 1979. "Comparison of Ionic Selectivity of Batrachotoxin-Activated Channels with Different Tetrodotoxin Dissociation Constants." *The Journal of General Physiology* 73 (6): 839–854. https://doi.org/10.1085/jgp.73.6.839.

Islam, M. T., and M. S. Mubarak. 2020. "Pyrrolidine Alkaloids and Their Promises in Pharmacotherapy." *Advances in Traditional Medicine* 20 (1): 13–22. https://doi.org/10.1007/s13596-019-00419-4.

Izzati, F., M. F. Warsito, A. Bayu, A. Prasetyoputri, A. Atikana, L. Sukmarini, S. I. Rahmawati, and M. Y. Putra. 2021. "Chemical Diversity and Biological Activity of Secondary Metabolites Isolated from Indonesian Marine Invertebrates." *Molecules* 26 (7): 1898. https://doi.org/10.3390/molecules26071898.

Jeckel, A. M., S. K. Bolton, K. R. Waters, M. M. Antoniazzi, C. Jared, K. Matsumura, K. Nishikawa, Y. Morimoto, T. Grant, and R. A. Saporito. 2022. "Dose-Dependent Alkaloid Sequestration and N-Methylation of Decahydroquinoline in Poison Frogs." *Journal of Experimental Zoology Part A: Ecological and Integrative Physiology* 337 (5): 537–546. https://doi.org/10.1002/jez.2587.

Jeckel, A. M., S. Kocheff, R. A. Saporito, and T. Grant. 2019. "Geographically Separated Orange and Blue Populations of the Amazonian Poison Frog *Adelphobates Galactonotus* (Anura, Dendrobatidae) Do Not Differ in Alkaloid Composition or Palatability." *Chemoecology* 29 (5–6): 225–234. https://doi.org/10.1007/s00049-019-00291-3.

Karle, I. L. 1973. "The Structure of Dihydroisohistrionicotoxin, a Unique Unsaturated Alkaloid and Anticholinergic Agent." *Journal of the American Chemical Society* 5:4036–4040. https://doi.org/10.1021/ja00793a034.

Kato, G., M. Glavinovic, J. Henry, K. Krnjevic, E. Puil, and B. Tattrie. 1975. "Actions of Histrionicotoxin on Acetylcholine Receptors." ISSN 0011-1643 *Croatica Chemica Acta* 47:439–447. https://hrcak.srce.hr/196635 .

Kayaalp, S. O., E. X. Albuquerque, and J. E. Warnick. 1970. "Ganglionic and Cardiac Actions of Batrachotoxin." *European Journal of Pharmacology* 12 (1): 10–18. https://doi.org/10.1016/0014-2999(70)90023-3.

Khan, I. M., T. L. Yaksh, and P. Taylor. 1997. "Epibatidine Binding Sites and Activity in the Spinal Cord." *Brain Research* 753 (2): 269–282. https://doi.org/10.1016/S0006-8993(97)00031-0.

Lapa, A. J., E. X. Albuquerque, J. M. Sarvey, J. Daly, and B. Witkop. 1975. "Effects of Histrionicotoxin on the Chemosensitive and Electrical Properties of Skeletal Muscle." *Experimental Neurology* 47 (3): 558–580. https://doi.org/10.1016/0014-4886(75)90088-6.

Li, H.-L., D. Hadid, and D. S. Ragsdale. 2002. "The Batrachotoxin Receptor on the Voltage-Gated Sodium Channel is Guarded by the Channel Activation Gate." *Molecular Pharmacology* 61 (4): 905–912. https://doi.org/10.1124/mol.61.4.905.

Linford, N. J., A. R. Cantrell, Y. Qu, T. Scheuer, and W. A. Catterall. 1998. "Interaction of Batrachotoxin with the Local Anesthetic Receptor Site in Transmembrane Segment IVS6 of the Voltage-Gated Sodium Channel." *Pharmacology* 95:13947–13952. https://doi.org/10.1073/pnas.95.23.13947.

Liu, D. M., B. Xu, and C. Dong. 2021. "Recent Advances in Colorimetric Strategies for Acetylcholinesterase Assay and Their Applications." *TrAC - Trends in Analytical Chemistry* 142:116320. https://doi.org/10.1016/j.trac.2021.116320.

MacFoy, C., D. Danosus, R. Sandit, T. H. Jones, H. M. Garraffo, T. F. Spande, and J. W. Daly. 2005. "Alkaloids of Anuran Skin: Antimicrobial Function?" *Zeitschrift für Naturforschung C* 60 (11–12): 932–937. https://doi.org/10.1515/znc-2005-11-1218.

Mans, D. R. A., J. Djotaroeno, M. Pawirodihardjo, and P. Friperson. 2021. "Exploring the Global Animal Biodiversity in the Search for New Drugs -Amphibians." *Journal Translational Science* 7 (6): 1–17. https://doi.org/10.15761/jts.1000411.

Marucci, G., M. Buccioni, D. Dal Ben, C. Lambertucci, R. Volpini, and F. Amenta. 2021. "Efficacy of Acetylcholinesterase Inhibitors in Alzheimer's Disease." *Neuropharmacology* 190:108352. https://doi.org/10.1016/j.neuropharm.2020.108352.

Masukawa, L. M., and E. X. Albuquerque. 1978. "Voltage- and Time-Dependent Action of Histrionicotoxin on the Endplate Current of the Frog Muscle." *The Journal of General Physiology* 72 (3): 351–367. https://doi.org/10.1085/jgp.72.3.351.

Mebs, D., J. V. Alvarez, W. Pogoda, S. W. Toennes, and G. Köhler. 2014. "Poor Alkaloid Sequestration by Arrow Poison Frogs of the Genus *Phyllobates* from Costa Rica." *Toxicon* 80:73–77. https://doi.org/10.1016/j.toxicon.2014.01.006.

Mensah-Dwumah, M., and J. W. Daly. 1968. "Pharmacological Activity of Alkaloids from Poison-Dart Frogs (Dendrobatidae)." *Toxicon* 16 (2): 189–194. https://doi.org/10.1016/0041-0101(78)90037-5.

Mina, A. E., A. K. Ponti, N. L. Woodcraft, E. E. Johnson, and R. A. Saporito. 2015. "Variation in Alkaloid-Based Microbial Defenses of the Dendrobatid Poison Frog *Oophaga Pumilio*." *Chemoecology* 25 (4): 169–178. https://doi.org/10.1007/s00049-015-0186-5.

Mortari, M. R., E. N. F. Schwartz, C. A. Schwartz, O. R. Pires, M. M. Santos, C. Bloch, and A. Sebben. 2004. "Main Alkaloids from the Brazilian Dendrobatidae Frog *Epipedobates flavopictus*: Pumiliotoxin 251D, Histrionicotoxin and Decahydroquinolines." *Toxicon* 43 (3): 303–310. https://doi.org/10.1016/j.toxicon.2004.01.001.

Narahashi, T., and T. Deguchi. 1970. "Effects of Batrachotoxin on Nerve Membrane Potential and Conductances." *Nature: New Biology* 229 (7): 221–222. https://doi.org/10.1038/newbio229221b0.

Newman, D. J., and G. M. Cragg. 2020. "Natural Products as Sources of New Drugs Over the Nearly Four Decades from 01/1981 to 09/2019." *Journal of Natural Products* 83 (3): 770–803. https://doi.org/10.1021/acs.jnatprod.9b01285.

Protti-Sánchez, F., L. Quirós-Guerrero, V. Vásquez, B. Willink, M. Pacheco, E. León, H. Pröhl, and F. Bolaños. 2019. "Toxicity and Alkaloid Profiling of the Skin of the *Golfo Dulcean* Poison Frog *Phyllobates Vittatus* (Dendrobatidae)." *Journal of Chemical Ecology* 45 (11–12): 914–925. https://doi.org/10.1007/s10886-019-01116-x.

Qian, C., T. Li, T. Y. Shen, L. Libertine-Garahan, J. Eckman, T. Biftu, and S. Ip. 1993. "Epibatidine is a Nicotinic Analgesic." *European Journal of Pharmacology* 250 (3): R13–R14. https://doi.org/10.1016/0014-2999(93)90043-H.

Rodríguez-Saona, C. 2012. Cap 13: La Ecología Química de Interacciones Tri-TróficasIn Temas Selectos en Ecología Química de Insectos. *El Colegio de la Frontera Sur. México-MX: Ecosur*, edited by J. C. Rojas, and A. Malo, 315–332.

Roseen, J. S., and F. A. Fuhrman. 1971. "Comparison of the Effects of Atelopidtoxin with the of Tetrodotoxin, Saxitoxin and Batrachotoxin on Beating of Cultured Chick Heart Cells." *Toxicon* 9 (4): 411–415. https://doi.org/10.1016/0041-0101(71)90140-1.

Rupniak, N. M. J., S. Patel, R. Marwood, J. Webb, J. R. Traynor, J. Elliott, S. B. Freedman, S. R. Fletcher, and R. G. Hill. 1994. "Antinociceptive and Toxic Effects of (+)-Epibatidine Oxalate Attributable to Nicotinic Agonist Activity." *British Journal of Pharmacology* 113 (4): 1487–1493. https://doi.org/10.1111/j.1476-5381.1994.tb17164.x.

Sakamoto, J., and H. Ishikawa. 2022. "Bioinspired Transformations Using Strictosidine Aglycones: Divergent Total Syntheses of Monoterpenoid Indole Alkaloids in the Early Stage of Biosynthesis." *Chemistry – A European Journal* 28 (10): e202200315. https://doi.org/10.1002/chem.202104052.

Sandeep, C., B. Padmashali, K. N. Venugopala, R. S. Kulkarni, R. Venugopala, and B. Odhav. 2016. "Synthesis and Characterization of Ethyl 7-Acetyl-2-Substituted 3-(Substituted Benzoyl) Indolizine-1-Carboxylates for *In Vitro* Anticancer Activity." *Asian Journal of Chemistry* 28 (5): 1043–1048. https://doi.org/10.14233/ajchem.2016.19582.

Santos, L., C. Oliveira, B. M. Vasconcelos, D. Vilela, L. Melo, L. Ambrósio, A. Silva, et al. 2021. "Good Management Practices of Venomous Snakes in Captivity to Produce Biological Venom-Based Medicines: Achieving Replicability and Contributing to Pharmaceutical Industry." *Journal of Toxicology and Environmental Health - Part B* 24 (1): 30–50. https://doi.org/10.1080/10937404.2020.1855279.

Saporito, R. A., M. A. Donnelly, P. Jain, H. M. Garraffo, T. F. Spande, and J. W. Daly. 2007. "Spatial and Temporal Patterns of Alkaloid Variation in the Poison Frog *Oophaga Pumilio* in Costa Rica and Panama Over 30 Years." *Toxicon* 50 (6): 757–778. https://doi.org/10.1016/j.toxicon.2007.06.022.

Saporito, R. A., M. A. Donnelly, T. F. Spande, and H. M. Garraffo. 2012. "A Review of Chemical Ecology in Poison Frogs." *Chemoecology* 22 (3): 159–168. https://doi.org/10.1007/s00049-011-0088-0.

Scherlach, K., and C. Hertweck. 2021. "Mining and Unearthing Hidden Biosynthetic Potential." *Nature Communications* 12 (1): 1–12. https://doi.org/10.1038/s41467-021-24133-5.

Seteyen, A. L. S., E. Girard-Valenciennes, A. Septembre-Malaterre, P. Gasque, P. Guiraud, and J. Sélambarom. 2022. "Anti-Alpha Viral Alkaloids: Focus on Some Isoquinolines, Indoles and Quinolizidines." *Molecules* 27 (16): 5080. https://doi.org/10.3390/molecules27165080.

Shan, L., Z. Liu, L. Ci, C. Shuai, X. Lv, and J. Li. 2019. "Research Progress on the Anti-Hepatic Fibrosis Action and Mechanism of Natural Products." *International Immunopharmacology* 75:105765. https://doi.org/10.1016/j.intimp.2019.105765.

Sheridan, R. E., S. S. Deshpande, F. J. Lebeda, and M. Adler. 1991. "The Effects of Pumiliotoxin-B on Sodium Currents in Guinea Pig Hippocampal Neurons." *Brain Research* 556 (1): 53–60. https://doi.org/10.1016/0006-8993(91)90546-8.

Shimizu, T., and K. Yokotani. 2009. "Brain Cyclooxygenase and Prostanoid TP Receptors are Involved in Centrally Administered Epibatidine-Induced Secretion of Noradrenaline and Adrenaline from the Adrenal Medulla in Rats." *European Journal of Pharmacology* 606 (1–3): 77–83. https://doi.org/10.1016/j.ejphar.2009.01.032.

Slagboom, J., C. Kaal, A. Arrahman, F. J. Vonk, G. W. Somsen, J. J. Calvete, W. Wüster, and J. Kool. 2022. "Analytical

Strategies in Venomics." *Microchemical Journal, Devoted to the Application of Microtechniques in All Branches of Science* 175:1–22. https://doi.org/10.1016/j.microc.2022.107187.

Souza, J. M., B. D. C. Goncalves, M. V. Gomez, L. B. Vieira, and F. M. Ribeiro. 2018. "Animal Toxins as Therapeutic Tools to Treat Neurodegenerative Diseases." *Frontiers in Pharmacology* 9:145. https://doi.org/10.3389/fphar.2018.00145.

Spinelli, R., F. M. Aimaretti, J. A. López, and A. S. Siano. 2019. "Amphibian Skin Extracts as Source of Bioactive Multi-Target Agents Against Different Pathways of Alzheimer's Disease." *Natural Product Research* 35 (4): 686–689. https://doi.org/10.1080/14786419.2019.1591396.

Tan, C. H. 2022. "Snake Venomics: Fundamentals, Recent Updates, and a Look to the Next Decade." *Toxins* 14 (4): 247. https://doi.org/10.3390/toxins14040247.

Tokuyama, T., J. Daly, and B. Witkop. 1969. "Structure of Batrachotoxin, a Steroidal Alkaloid from the Colombian Arrow Poison Frog, *Phyllobates aurotaenia*, and Partial Synthesis of Batrachotoxin and Its Analogs and Homologs." *Journal of the American Chemical Society* 91 (14): 3931–3938. https://doi.org/10.1021/ja01042a042.

Toma, T., M. M. Logan, F. Menard, A. S. Devlin, and J. Bois. 2016. "Inhibition of Sodium Ion Channel Function with Truncated Forms of Batrachotoxin." *ACS Chemical Neuroscience* 7 (10): 1463–1468. https://doi.org/10.1021/acschemneuro.6b00212.

Tricco, A. C., E. Lillie, W. Zarin, K. K. O'Brien, H. Colquhoun, D. Levac, D. Moher, et al. 2018. "PRISMA Extension for Scoping Reviews (PRISMA-Scr): Checklist and Explanation." *Annals of Internal Medicine* 169 (7): 467–473. https://doi.org/10.7326/M18-0850.

Vandendriessche, T., Y. Abdel-Mottaleb, C. Maertens, E. Cuypers, A. Sudau, U. Nubbemeyer, D. Mebs, and J. Tytgat. 2008. "Modulation of Voltage-Gated Na+ and K+ Channels by Pumiliotoxin 251D: A "Joint venture" Alkaloid from Arthropods and Amphibians." *Toxicon* 51 (3): 334–344. https://doi.org/10.1016/j.toxicon.2007.10.011.

Wainwright, C. L., M. M. Teixeira, D. L. Adelson, E. J. Buenz, B. David, K. B. Glaser, Y. Harata-Lee, et al. 2022. "Future Directions for the Discovery of Natural Product-Derived Immunomodulating Drugs: An IUPHAR Positional Review." *Pharmacological Research: The Official Journal of the Italian Pharmacological Society* 177:106076. https://doi.org/10.1016/j.phrs.2022.106076.

Wang, S. Y., and G. K. Wang. 2017. "Single Rat Muscle Na+ Channel Mutation Confers Batrachotoxin Autoresistance Found in Poison-Dart Frog *Phyllobates Terribilis*." *Proceedings of the National Academy of Sciences of the United States of America* 114 (39): 10491–10496. https://doi.org/10.1073/pnas.1707873114.

Wang, J., J. Zhao, S. Guo, C. North, and N. Ramakrishnan. 2020. "ReCloud: Semantics-Based Word Cloud Visualization of User Reviews." In *Graphics Interface 2014*, 151–158. AK Peters/CRC Press.

Weldon, P. J., Y. J. Cardoza, R. K. van der Meer, W. C. Hoffmann, J. W. Daly, and T. F. Spande. 2013. "Contact Toxicities of Anuran Skin Alkaloids Against the Fire Ant (*Solenopsis Invicta)*." *Naturwissenschaften* 100 (2): 185–192. https://doi.org/10.1007/s00114-013-1010-0.

Weldon, P. J., M. Kramer, S. Gordon, T. F. Spande, and J. W. Daly. 2006. "A Common Pumiliotoxin from Poison Frogs Exhibits Enantioselective Toxicity Against Mosquitoes." *Proceedings of the National Academy of Sciences* 103 (47): 17818–17821. https://doi.org/10.1073/pnas.0608646103.

Wu, X., Z. Liu, X. Yu, S. Xu, and J. Luo. 2020. "Autophagy and Cardiac Diseases: Therapeutic Potential of Natural Products." *Medicinal Research Reviews* 41 (1): 314–341. https://doi.org/10.1002/med.21733.

Zhang, Y. 2015. "Why Do We Study Animal Toxins?" *Zoological Research* 36:183–222. https://doi.org/10.13918/j.issn.2095-8137.2015.4.183.

Zhang, J., S. L. Morris-Natschke, D. Ma, X. F. Shang, C. J. Yang, Y. Q. Liu, and K. H. Lee. 2020. "Biologically Active Indolizidine Alkaloids." *Research Reviews United States Office of Naval Research* 41 (2): 928–960. https://doi.org/10.1002/med.21747.